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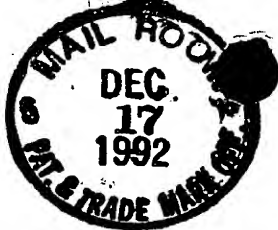
TO ALL WHOM IT MAY CONCERN:

Be it known that WE, CHRISTER CARL GUSTAV CARLING and JAN WILLIAM TROFAST, citizens of Sweden, residing at Backvägen 8, S-240 10 Dalby, Sweden, and Vapenkroken 34, S-226 47 Lund, Sweden, respectively, have invented an improvement in

NEW COMBINATION OF A BRONCHODILATOR AND A STERIOIDAL
ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY
DISORDERS, AS WELL AS ITS USE AND THE PREPARATION THEREOF

of which the following is a

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New combination of a bronchodilator and a ^{steroidal} ~~steroidal~~ anti-inflammatory drug for the treatment of respiratory disorders, as well as its use and the preparation thereof.

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Field of the invention

10 This invention relates to improvements in the treatment of mild as well as severe asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator in combination with a steroidal anti-inflammatory drug for the treatment of respiratory
15 disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients. It emphasizes the use of a long-acting bronchodilator which provides rapid relief of symptoms.

20 Background of the invention

There have recently been significant advances in our understanding of asthma. Despite many advances, both in awareness of the disease by doctors and patients alike,
25 coupled with the introduction of very powerful and effective anti-asthma drugs, asthma remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the most important feature of asthma. Recently there has
30 been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving ^{irreversible} ~~irreversible~~ narrowing of the airways and
35 fibrosis of the lung tissue. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating

the underlying inflammation.

c 5 The most common cause for poor control of asthma is poor compliance with the long-term management of chronic asthma, particularly with ^{prophylactic} prophylactic treatments, such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β_2 -agonist inhalers, since these provide rapid relief of symptoms, but often do not take prophylactic therapy, such as inhaled
10 steroids, regularly because there is no immediate symptomatic benefit. They also counteract down regulation of β_2 -adrenoceptor agonists.

15 Formoterol, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide), is an adrenoceptor agonist which selectively stimulates β_2 -receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by
20 endogenous mediators, and increased mucociliary ^{clearance} clearance. Inhaled formoterol fumarate acts rapidly, usually within minutes which gives the patient immediate confirmation that he has taken an ^{adequate} adequate dose and thereby avoiding overdosing of both β -agonist and
25 steroid. Inhaled formoterol also exerts a prolonged bronchodilation, which in clinical trials has been demonstrated as up to 12 hours.

30 Budesonide, (16,17-butyridenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione), may be given in a high inhaled dose (up to 2 mg daily) with very low systemic effects, possibly because of its rapid metabolism. The high rapid systemic elimination of
35 budesonide is due to extensive and rapid hepatic metabolism. Long term clinical studies have shown that inhaled budesonide is a pharmacologically safe drug. High doses of inhaled budesonide are highly effective and well

tolerated when used in oral steroid replacement therapy. Budesonide represents a logical safe and effective therapy for long term control of asthma.

5 The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects. The drawbacks of the currently available bronchodilators are their
 10 relatively short duration of action. By using a compound with long duration e.g. formoterol it would be possible to avoid the nocturnal asthma, which so often causes considerable anxiety and debility to the patients. Formoterol gives less nocturnal waking than the commonly
 15 used short-acting agonists like salbutamol, terbutaline and the like. Formoterol has been registered for oral administration in Japan since 1986.

Pharmaceutical combinations of long-acting β_2 -agonists
 20 and steroids are disclosed in two European applications, EP 416950 which discloses the combination of salmeterol and beclomethasone, and EP 416951 which discloses the combination of salmeterol and fluticasone propionate.

25 In Ann. Allergy 1989, 63 (3), p. 220-224 the use of a β_2 -agonist, i.e. formoterol and a steroid, i.e. budesonide ^{separately} ~~separately~~ are mentioned. ^{Not} ~~It is not~~ disclosed ^{is} a pharmaceutical combination including both formoterol and budesonide, or the use of the two compounds in
 30 combination therapy. The use of a β_2 -agonist and a steroid ^{mentioned} ~~separately~~ is also ~~mentioned~~ in Lung (1990), 168, no. supp, p. 105-110.

Outline of the Invention

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The present invention is based on the concept of a novel combination therapy whereby formoterol (and/or a

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physiologically acceptable salt and/or solvate thereof)
 and budesonide are ^{administered} ~~administered~~ simultaneously,
 sequentially or ^{separately} ~~separately~~ by inhalation. This

combination has not only a greater efficiency and
 5 duration of bronchodilator action but the combination
 also has a rapid onset of action. This new feature is of
 utmost importance in order to establish a higher
 compliance for patients and it provides a rescue medicine
 thereby avoiding the necessity for the patient of
 10 carrying two different inhalers. This simplifies life for
 patients considerably and makes life more comfortable and
 secure. The rapid onset of the long-acting β_2 -agonist
 gives the patient immediate confirmation that he has
 taken an adequate dose and thereby avoiding overdosing of
 15 both β_2 -agonist and steroid. Since the use of formoterol
 instead of salmeterol gives a much more rapid onset the
 combinations according to the invention have a number of
 advantages compared to the combinations disclosed i EP
 416950 and EP 41651. The combination according to present
 20 invention permits a twice daily dosing regime as a basic
 treatment of asthma, particularly nocturnal asthma.

The present invention provides a medicament containing,
 separately, or together, (i) formoterol (and/or a
 25 physiologically acceptable salt and/or solvate thereof)
 and (ii) budesonide for simultaneous, sequential or
 separate administration by inhalation in the treatment of
 respiratory ^{disorders} ~~disorder~~.

30 The invention also provides a pharmaceutical composition
 for administration by inhalation in the treatment of
 respiratory ^{disorders} ~~disorder~~ which composition comprises
 formoterol (and/or a physiologically acceptable salt
 and/or solvate thereof) and budesonide.

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According to another aspect of the invention there are
 provided pharmaceutical compositions comprising effective

amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide as a combined ^{preparation} ~~preparation~~ for simultaneous, sequential or ^{separate} ~~separate~~ administration by inhalation in the treatment of respiratory ^{disorders} ~~disorder~~.

The invention further provides formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide for use in combination therapy by simultaneous, sequential or ^{separate} ~~separate~~ administration by inhalation in the treatment of respiratory ^{disorders} ~~disorder~~.

Further the invention provides the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or ^{separately} ~~separately~~ by inhalation in the treatment of respiratory ^{disorders} ~~disorder~~ and the use of budesonide in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or ^{separately} ~~separately~~ by inhalation in the treatment of respiratory ^{disorders} ~~disorder~~.

The invention additionally relates to the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of a medicament for combination therapy for simultaneous, sequential or ^{separate} ~~separate~~ administration of formoterol and budesonide by inhalation in the treatment of respiratory ^{disorders} ~~disorder~~.

According to a further feature of the invention there is provided a method of treating respiratory ^{disorders} ~~disorder~~ which comprises the simultaneous, sequential or separate

administration by inhalation of effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

5 Suitable physiologically salts of formoterol include acid
addition salts derived from inorganic and organic acids,
such as the hydrochloride, hydrobromide,
sulphate, phosphate, maleate, fumarate, tartrate,
citrate, benzoate, 4-methoxybenzoate, 2- or 4-
10 hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate,
methanesulphonate, ascorbate, salicylate, acetate
succinate, lactate, glutarate, gluconate,
tricarballate, hydroxynaphthalenecarboxylate or oleate.
Formoterol is preferably used in the form of its fumarate
15 salt and as a dihydrate.

The ratio of formoterol to budesonide used according to
the invention is preferably within the range of 1:4 to
1:70. The two drugs may be administered separately in the
20 same ratio.

The intended dose regimen is a twice daily
administration, where the suitable daily dose of
formoterol is in the range of 6 to 100 µg with a
25 preferred dose of 6-48 µg and the suitable daily dose for
budesonide is 50 to 4800 µg with a preferred dose of 100-
1600 µg. The particular dose used will strongly depend on
the patient (age, weight etc) and the severity of the
disease (mild, moderate, severe asthma etc).

30 For administration, the combination is suitably inhaled
from a nebulizer, from a pressurized metered dose inhaler
or as a dry powder from a dry powder inhaler (e.g. as
sold under the trade mark Turbuhaler) or from a dry
35 powder inhaler utilizing ^{gelatin} ~~gelatine~~, plastic or other
capsules, cartridges or blister packs.

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A diluent or carrier, generally non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powdered medicament.

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Examples of the preparation of suitable dosage forms according to the invention include the following:

Formoterol fumarate dihydrate and budesonide (optionally premicronized) are mixed in the proportions given above.

10 The agglomerated, free-flowing micronized mixture may be filled into ^a dry powder inhaler such as sold under the trade mark Turbuhaler. When a capsule system ^{is used} ~~issued~~, it is desirable to include a filler in the mixture.

15 The micronized mixture may be suspended or dissolved in a liquid propellant mixture which is kept in a container that is sealed with a metering valve and fitted into a plastic actuator. The propellants used may be chlorofluorocarbons of different chemical formulae. The most frequently used chlorofluorocarbon propellants are trichloromonofluoromethane (propellant 11), dichloro-

20 difluoromethane (propellant 12),, dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (propellant 134a) and 1,1-~~di~~^{diffuoro}fluoroethane (propellant 152a). Low concentrations of a surfactant such as sorbitan trioleate, lecithin, disodium dioctylsulphosuccinate or oleic acid may also be used to improve the physical stability.

30 The invention is further illustrated by way of example with reference to the following Examples.

Example 1 - Dry Powder Inhaler (Turbuhaler)

35	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	200 µg

TOO BOX

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The storage unit of the inhaler is filled with sufficient ^{material} for at least 200 doses.

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5	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	24 µg
	Budesonide	200 µg
	The storage unit is filled with sufficient ^{material} for at least 200 doses.	

T0091X

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10	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	100 µg
	The storage unit is filled with sufficient ^{material} for at least 200 doses.	
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Example 2 - Metered dose inhaler

T0092X

	<u>Active ingredient</u>	<u>Per dose</u>
20	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	200 µg
	Stabilizer	0.1 - 0.7 mg
	Propellant	25 - 100 µl

25	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	24 µg
	Budesonide	200 µg
	Stabilizer	0.1 - 0.7 mg
30	Propellant	25 - 100 µl

35	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	200 µg
	Stabilizer	0.1 - 0.7 mg
	Propellant	25 - 100 µl

Example 3 - Metered dose dry powder formulation

	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
5	Budesonide	200 µg
	Lactose	up to 5, 12.5 or 25 mg

	<u>Active ingredient</u>	<u>Per dose</u>
10	Formoterol (as fumarate dihydrate)	24 µg
	Budesonide	200 µg
	Lactose	up to 5, 12.5 or 25 mg

TO100X

15	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	100 µg
	Lactose	up to 5, 12.5 or 25 mg